7-SUBSTITUTED 3-NITRO-PYRAZOLO '1,5-A! PYRIMIDINES

Technical field

This invention is directed to agents with affinity for $GABA_A$ receptor, more specifically to pyrazolo[1,5-a] pyrimidines.

Background of the invention

$GABA_A$ receptor (γ-aminobutyric $acid_A$) is a pentameric protein which forms a membrane ion channel. $GABA_A$ receptor is implicated in the regulation of sedation, anxiety, muscle tone, epileptogenic activity and memory functions. These actions are due to defined subunits of $GABA_A$ receptor, particularly the α_1- and α_2-subunits.

Sedation is modulated by the α1-subunit. Zolpidem is characterized by a high affinity for the α1-receptors and its sedative and hypnotic action is mediated by these receptors in vivo. Similarly, the hypnotic action of zaleplon is also mediated by the α1-receptors.

The anxiolytic action of diazepam is mediated by the enhancement of GABAergic transmission in a population of neurons expressing the α_2-receptors. This indicates that the α_2-receptors are highly specific targets for the treatment of anxiety.

Muscle relaxation in diazepam is mainly mediated by α_2-receptors, since these receptors exhibit a highly specific expression in spinal cord.

The anticonvulsant effect of diazepam is partly due to α_1-receptors. In diazepam, a memory-impairing compound, anterograde amnesia is mediated by α_1-receptors.

$GABA_A$ receptor and its α_1- and α_2-subunits have been widely reviewed by H. Möhler et al.(J. Pharmacol. Exp. Ther., 300, 2-8, 2002); H. Möhler et al.(Curr. Opin. Pharmacol., 1, 22-25, 2001); U. Rudolph et al.(Nature, 401, 796-800, 1999); and D. J. Nutt et al. (Br. J. Psychiatry, 179, 390-396, 2001).

Diazepam and other classical benzodiazepines are extensively used as anxiolytic agents, hypnotic agents, anticonvulsants and muscle relaxants. Their side effects include anterograde amnesia, decrease in motor activity and potentiation of ethanol effects.

In this context, the compounds of this invention are ligands of α_1- and α_2-$GABA_A$ receptor for their clinical application in sleep disorders, preferably insomnia, anxiety and epilepsy.

Insomnia is a highly prevalent disease. Its chronicity affects 10% of the population and 30% when transitory insomnia is computed as well. Insomnia describes the trouble in getting to sleep or staying asleep and is associated with hangover effects the next day such as weariness, lack of energy, low concentration and

irritability. The social and health impact of this complaint is important and results in evident socioeconomic repercussions.

Pharmacological therapy in the management of insomnia firstly included barbiturates and chloral hydrate, but these drugs elicit numerous known adverse effects, for example, overdose toxicity, metabolic induction, and enhanced dependence and tolerance. In addition, they affect the architecture of sleep by decreasing above all the duration and the number of REM sleep stages. Later, benzodiazepines meant an important therapeutic advance because of their lower toxicity, but they still showed serious problems of dependence, muscle relaxation, amnesia and rebound insomnia following discontinuation of medication.

The latest known therapeutic approach has been the introduction of non-benzodiazepine hypnotics, such as pyrrolo[3,4-b]pyrazines (zopiclone), imidazo[1,2-a] pyridines (zolpidem) and, finally, pyrazolo[1,5-a] pyrimidines (zaleplon). Later, two new pyrazolo[1,5-a] pyrimidines, indiplon and ocinaplon, have entered into development, the latter with rather anxiolytic action. All these compounds show a rapid sleep induction and have less hangover effects the next day, lower potential for abuse and lower risk of rebound insomnia than benzodiazepines. The mechanism of action of these compounds is the alosteric activation of $GABA_A$ receptor through its binding to benzodiazepine binding site (C. F. P. George, The Lancet, 358, 1623-1626, 2001). While benzodiazepines are unspecific ligands at $GABA_A$ receptor binding site, zolpidem and zaleplon show a greater

selectivity for α_1-subunit. Notwithstanding that, these drugs still affect the architecture of sleep and may induce dependence in long-term treatments.

In US patent documents No. 4,626,538 and No. 6,399,621, and European Patent No. 129,847 hypnotic pyrazolo[1,5-a] pyrimidines are disclosed. These patents correspond to zaleplon, indiplon and ocinaplon, respectively.

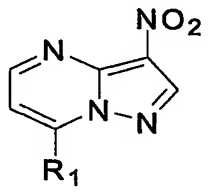
Research for new active compounds in the management of insomnia answers an underlying health need, because even recently introduced hypnotics still affect the architecture of sleep and may induce dependence in long-term treatments.

It is therefore desirable to focus on the development of new hypnotic agents with a lower risk of side effects.

Thus, the present invention is directed to new 7-substituted 3-nitro-pyrazolo[1,5-a]pyrimidines which are active versus $GABA_A$ receptor and, particularly, versus its α_1- and α_2-subunits. Consequently, the compounds of this invention are useful in the treatment and prevention of all those diseases mediated by α_1- and α_2-$GABA_A$ receptor. Non-limitative examples of such diseases are sleep disorders, preferably insomnia, anxiety and epilepsy. Non-limitative examples of the relevant indications of the compounds of this invention are all those diseases or conditions that need an induction of sleep, such as insomnia or anesthesia, an induction of sedation or an induction of muscle relaxation.

Detailed description of the invention

The present invention relates to novel 7-substituted 3-nitro-pyrazolo[1,5-a]pyrimidines of general formula (I):

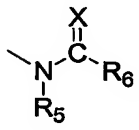
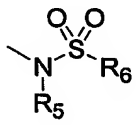
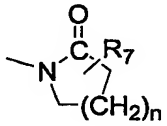


(I)

wherein

R_1 is selected from the group consisting of phenyl, pyridyl, pyrimidinyl, triazinyl, N-oxide-pyridyl, thienyl, furyl, thiazolyl and oxazolyl, each R_1 being optionally substituted with an R_2 group;

R_2 is selected from the group consisting of alkyl(C_1-C_6), cycloalkyl(C_3-C_6), alkenyl(C_2-C_6), alkynyl(C_2-C_6), alkoxy(C_1-C_6), CF_3, CN, SO_2-R_3, NO_2, NH-R_3, NR_3R_4, COR_5, CO-NHR_5, $COOR_5$,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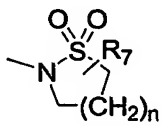

;

R_3 and R_4 are independently selected from the group vconsisting of alkyl(C_1-C_6), cycloalkyl(C_3-C_6), aryl and heteroaryl;

R_5 is selected from the group consisting of hydrogen, alkyl(C_1-C_6), alkenyl(C_2-C_6), alkynyl(C_2-C_6) and cycloalkyl(C_3-C_6);

R_6 is selected from the group consisting of alkyl(C_1-C_6), cycloalkyl(C_3-C_6), alkoxy(C_1-C_6), NH-alkyl(C_1-C_6), N(dialkyl(C_1-C_6)), alkyl(C_1-C_6)-O-alkyl(C_1-C_6), alkyl(C_1-

C_6)-NH-alkyl(C_1-C_6), alkyl(C_1-C_6)-N(dialkyl(C_1-C_6)), phenyl, monosubstituted phenyl, furyl, thienyl, thiazolyl and pyridyl;

R_7 is selected from the group consisting of hydrogen, alkyl(C_1-C_6), cycloalkyl(C_3-C_6), aryl and substituted or unsubstituted heteroaryl;

R_8 is selected from the group consisting of hydrogen, alkyl(C_1-C_6), CF_3, CN, CO-R_9 and SO_2-R_9;

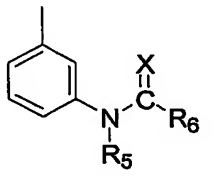
R_9 is selected from the group consisting of hydrogen, alkyl(C_1-C_6), phenyl, substituted phenyl and substituted or unsubstituted heteroaryl;

X is O, S or NR_8; and

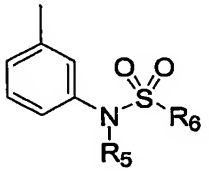
n is integer 1, 2 or 3;

and their pharmaceutically acceptable salts.

In particular, the present invention relates to novel pyrazolo[1,5-a]pyrimidines of formula (I) wherein R_1 is (i), (ii), (iii), (iv):



(i)



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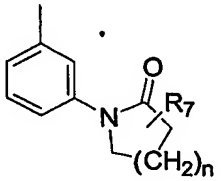
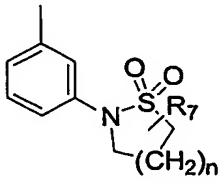


(iii)



(iv) ;

phenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, furan-2-yl, thiophen-2-yl, pyridin-2-yl, pyridin-3-yl and pyridin-4-yl.

Preferably, in (i) and (ii) R_5 is selected from alkyl (C_1-C_6), cycloalkyl(C_3-C_6) and alkynyl(C_2-C_6) and in (iii) and (iv) R_7 is H and n is 1 or 2.

More particularly, in (i) and (ii) R_5 is selected from the group consisting of methyl, ethyl, n-propyl, i-propyl, n-butyl, cyclopropyl and 2-propynyl; and R_6 is selected from the group consisting of methyl, ethyl, n-propyl, i-propyl, n-butyl, phenyl and 4-methoxy-phenyl; in (iii) and (iv) R_7 is hydrogen and n is 1; when X is NR_8, R_8 is selected from the group consisting of hydrogen, methyl and CN.

The term "aryl" preferably includes phenyl and naphthyl. "Heteroaryl" means 5- or 6-membered aromatic heterocyclic groups containing 1, 2, or 3 heteroatoms which independently of each other are selected from N, O and S. Examples for heteroaryl groups are pyridyl, pyrimidinyl, triazinyl, pyrrolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, furyl, thienyl, triazolyl.

Monosubstituted phenyl means that the phenyl group carries one substituent which is selected from alkyl(C_1-C_6), alkoxy(C_1-C_6), halogen, and CF_3.

Substituted phenyl and substituted heteroaryl means that the phenyl or heteroaryl group carries 1, 2 or 3 substituents which independently of each other are selected from alkyl(C_1-C_6), alkoxy(C_1-C_6), halogen, and CF_3. Substituted heteroaryl includes groups carrying said substituent(s) at a nitrogen heteroatom.

Halogen means fluoro, chloro, bromo, iodo and preferably fluoro and chloro.

Alkyl groups (also in alkoxy, NH-alkyl etc.) include straight chain and branched groups and preferably have 1 to 4 carbon atoms.

Preferred cycloalkyl groups are cyclopropyl, cyclopentyl and cyclohexyl.

The term "pharmaceutically acceptable salt" used herein encompasses any salt formed from organic and inorganic acids, such as hydrobromic, hydrochloric, phosphoric, nitric, sulfuric, acetic, adipic, aspartic, benzenesulfonic, benzoic, citric, ethanesulfonic, formic, fumaric, glutamic, lactic, maleic, malic, malonic, mandelic, methanesulfonic, 1,5-naphthalendisulfonic, oxalic, pivalic, propionic, p-toluenesulfonic, succinic, tartaric acids and the like.

The preferred compounds of the present invention are shown below:

N-ethyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-acetamide;

N-methyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-acetamide;

N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-propyl)-acetamide;

N-(n-butyl)-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-acetamide;

N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(2-propynyl)-acetamide;

3-nitro-7-phenyl-pyrazolo[1,5-a]pyrimidine;

3-nitro-7-(2-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;
3-nitro-7-(3-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;
3-nitro-7-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;
7-furan-2-yl-3-nitro-pyrazolo[1,5-a]pyrimidine;
3-nitro-7-thiophen-2-yl-pyrazolo[1,5-a]pyrimidine;
3-nitro-7-pyridin-2-yl-pyrazolo[1,5-a]pyrimidine;
3-nitro-7-pyridin-3-yl-pyrazolo[1,5-a]pyrimidine;
3-nitro-7-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine;
N-ethyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-methanesulfonamide;
N-ethyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-4-methoxy-benzenesulfonamide;
N-ethyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-benzenesulfonamide;
N-methyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-methanesulfonamide;
N-(n-butyl)-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-4-methoxy-benzenesulfonamide;
N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-propyl)-4-methoxy-benzenesulfonamide;
N-methyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-4-methoxy-benzenesulfonamide;
N-(n-butyl)-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-4-benzenesulfonamide;
N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-propyl)-benzenesulfonamide;
N-methyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-4-benzenesulfonamide;
N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-propyl)-methanesulfonamide;

N-(n-butyl)-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-methanesulfonamide;
1-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-pyrrolidin-2-one;
N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(prop-2-inyl)-methanesulfonamide;
N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-propyl)-ethanesulfonamide;
N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-ethyl)-ethanesulfonamide;
N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-prop-2-inyl)-propane-2-sulfonamide;
N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-ethanesulfonamide;
N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-butyl)-ethanesulfonamide;
7-(3-(2-isothiazolydinyl-1,1-dioxide)-phenyl)-3-nitro-pyrazolo[1,5-a]pyrimidine;
N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-propane-2-sulfonamide;
N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-propane-2-sulfonamide;
N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-butyl)-propane-2-sulfonamide; and
N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-propyl)-propane-2-sulfonamide.

Another embodiment of the present invention is to provide a process for preparing the compounds of formula (I) and their pharmaceutically acceptable salts.

Another embodiment of the present invention is to provide a method for treating or preventing diseases

associated with $GABA_A$ receptor modulation in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing diseases associated with α_1-$GABA_A$ receptor modulation in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing diseases associated with α_2-$GABA_A$ receptor modulation in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing anxiety in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing epilepsy in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing sleep disorders in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing insomnia in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for inducing sedation-hypnosis in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for inducing anesthesia in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for modulating the necessary time to induce sleep and its duration in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for inducing muscle relaxation in a

mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a pharmaceutical composition containing a compound of formula (I) or a pharmaceutically acceptable salt thereof in association with therapeutically inert carriers.

The compositions include those suitable for oral, rectal and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route will depend on the nature and severity of the condition being treated. The most preferred route of the present invention is the oral route. The compositions may be conveniently presented in unit dosage form, and prepared by any of the methods well known in the art of pharmacy.

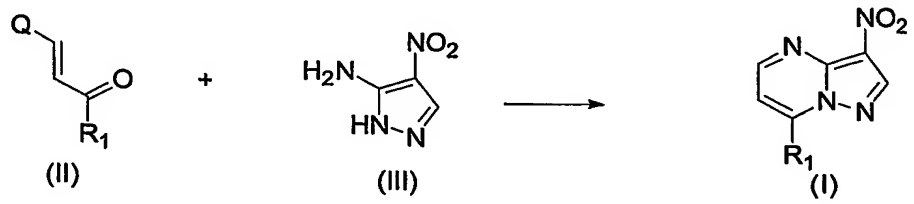
The active compound can be combined with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of the preparation desired for administration, e.g. oral or parenteral (including intravenous injections or infusions). In preparing the compositions for oral dosage form any of the usual pharmaceutical media may be employed. Usual pharmaceutical media include, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as for example, suspensions, solutions, emulsions and elixirs);

aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like, in the case of oral solid preparations (such as for example, powders, capsules, and tablets) with the oral solid preparations being preferred over the oral liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

A suitable dosage range for use is from about 0.01 mg to about 100,00 mg total daily dose, given as a once daily administration or in divided doses if required.

The compounds of general formula (I) may be prepared according to the reaction shown in Scheme 1.

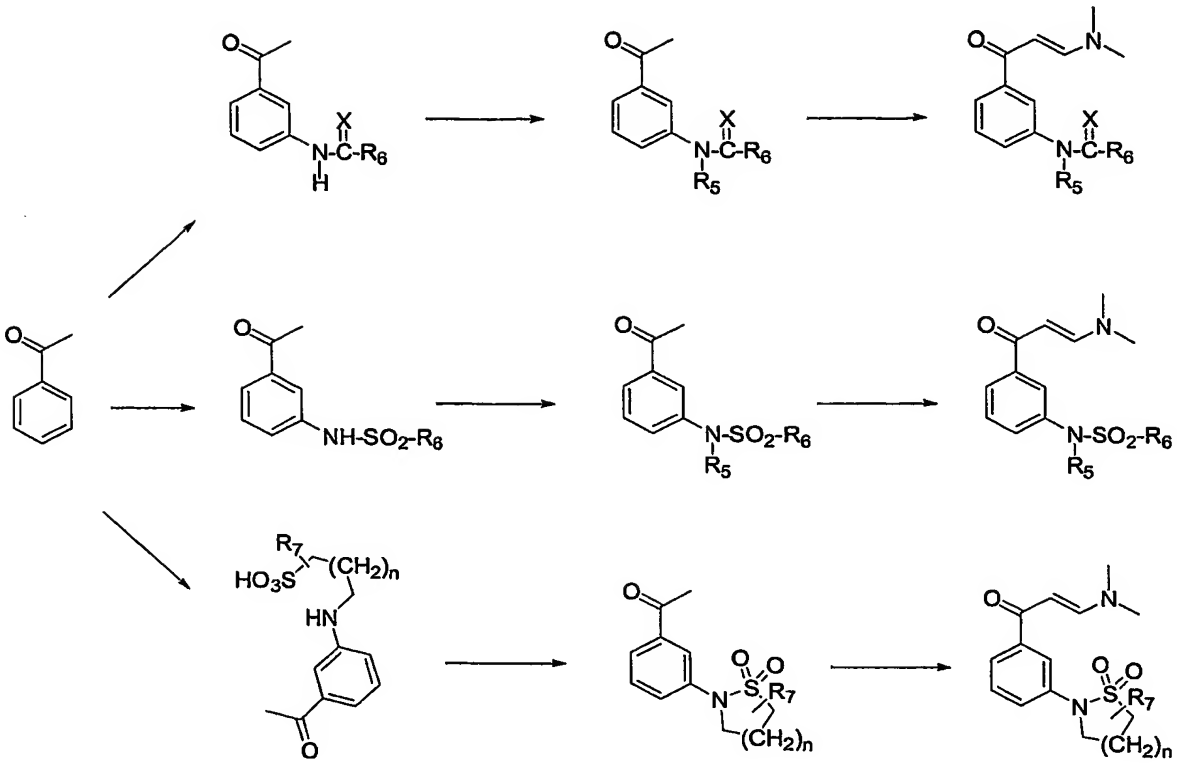


Scheme 1

where R_1 is as described above and Q is an appropriate leaving group consisting of dimethylamino, methylthio or methoxy. The reaction between 4-nitro-2H-pyrazol-3-ylamine (III) and appropriately substituted 1-(aryl) or (heteroaryl)-2-propen-1-one (II) is carried out in an

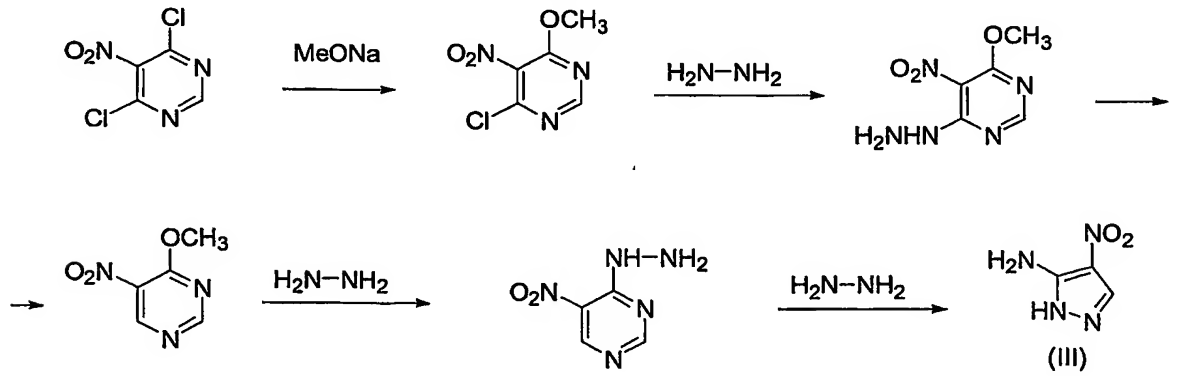
inert polar protic or aprotic solvent such as glacial acetic acid, ethanol, methanol, dimethylformamide or dimethylsulfoxide at a temperature ranging from 50° to 130°C. After elapsing several hours (reaction time), the solvent is removed and the residue obtained is partitioned between an aqueous solution of sodium bicarbonate and dichloromethane. The crude resulting from evaporating the organic layer to dryness may be purified by one of the following methods: (a) Silica gel chromatography using ethyl acetate or dichloromethane/methanol as eluent; and (b) Crystallization in a suitable solvent (for example, ethyl acetate, ethanol, methanol, etc.).

The intermediate of formula (II) when Q is dimethylamino may be obtained by reaction between the corresponding acetophenone and *N,N*-dimethylformamide dimethylacetal or Bredereck's reagent (*tert*-butoxybis(dimethylamino)methane) as described by J. M. Domagala et al (J. Heterocyclic Chem., 26(4), 1147-58, 1989); and K. Sawada et al (Chem. Pharm. Bull., 49(7), 799-813, 2001). Specifically, when R_1 is a substituted aryl group, the reaction sequence leading to the intermediate of formula (II) is shown in Scheme 2, R_5,R_6, R_7 and n being as described above.



Scheme 2

The intermediate 4-nitro-2H-pyrazol-3-ylamine (III) is obtained as described by M. E. C. Biffin et al. (J. Chem. Soc. (C) 2159-2162, 1968); M. E. C. Biffin et al. (Aust. J. Chem. 26, 1041-1047, 1967); and M. E. C. Biffin et al. (Tetrahedron Lett., 21, 2029-2031, 1967) following the reaction sequences shown in Scheme 3.



Scheme 3

From the compounds of general formula (I) it is possible to obtain their pharmaceutically acceptable salts by treatment with the corresponding acids.

The applicants have discovered that the compounds of the present invention have a high affinity for α_1- and α_2-$GABA_A$ receptors as shown in Tables 1 and 2. These *in vitro* results are consistent with those *in vivo* results obtained in sedation-hypnosis tests (Table 3). In accordance with the results obtained, certain compounds of the present invention have surprisingly evidenced pharmacological activity both *in vitro* and *in vivo*, which has been similar to or higher than that of prior-art compounds. All these results support their use in diseases or conditions modulated by α_1- and α_2-$GABA_A$ receptors, such as insomnia or anesthesia, in which an induction of sleep, an induction of sedation or an induction of muscle relaxation are needed.
The pharmacological activity of the compounds of the present invention has been determined as shown below.

Ligand-binding assays. Determination of the affinity of test compounds for α_1- and α_2-$GABA_A$ receptors.
Male Sprague-Dawley rats weighing 200-250 g at the time of experiment were used. After decapitation of the animal, the cerebellum (tissue that mostly contains α_1-$GABA_A$ receptor) and spinal cord (tissue that mostly contains α_2-$GABA_A$ receptor) were removed. The membranes were prepared according to the method by J. Lameh et al.(Prog. Neuro-Psychopharmacol. Biol. Psychiatry, 24,

979-991, 2000). Once the tissues weighed, they were suspended in 50 mM Tris HCl buffer, pH 7.7, (1:40 v/v), homogenized and then centrifuged at 20000 g for 10 min at 7°C. The resulting pellet was resuspended under the same conditions and centrifuged again. The final pellet obtained was resuspended on a minimum volume and kept at -80°C overnight. On the next day, the process was repeated until the final pellet was resuspended at a ratio of 1:10 (v/v).

The affinity of the compounds was determined by competitive tests using radiolabeled flumazenil as ligand. The methods described by S. Arbilla et al. (Eur. J. Pharmacol., 130, 257-263, 1986); and Y. Wu et al. (Eur. J. Pharmacol., 278, 125-132, 1995) were used. The membranes containing the study receptors, flumazenil (radiolabeling at a final concentration of 1 nM) and ascending concentrations of test compounds (in a total volume of 500 µl in 50 nM [ph 7.4] Tris HCl buffer) were incubated. Simultaneously, the membranes were only incubated with the radiolabeled flumazenil (total binding, 100%) and in the presence of an elevated concentration of unradiolabeled flumazenil (non-specific binding, % estimate of radiolabeled ligand). The reactions started on adding the radiolabeled ligand followed by incubation for 60 minutes at 0°C. At the end of the incubation period, the tubes were filtered using a Brandel Mod. M-48R harvester and then washed three times with cold test buffer. The harvester was fitted with a GF/B filter that retained the membranes containing the receptors and the radiolabeled ligand which had been bound to the receptors. Then the filters were removed and left till dry. Once dried, the filters were cut, placed in vials with scintillation liquid and

left under stirring overnight. The next day the filters were counted using a Packard Mod. Tricarb scintillation counter.

For analysis of the results the percentage of specific binding for every concentration of test compound was calculated as follows:

$$\% \text{ specific binding} = (X-N/T-N) \times 100$$

where,

X: amount of bound ligand for every concentration of compound.

T: total binding, maximum amount bound to the radiolabeled ligand.

N: Non-specific binding, amount of radiolabeled ligand bound in a non-specific way irrespective of the receptor used.

Every concentrations of compound were tested in duplicate and their mean values were used to determine the experimental values of % specific binding versus the concentration of compound. The values thus attained were fitted to a equation for competitive assays (SigmaPlot, SPSS Inc.) and the IC_{50} values (concentration of compound able to inhibit by 50% the specific binding) were calculated. Inhibition constants (K_i) were calculated from the IC_{50} values according to Cheng-Prusoff's formula (Y. Cheng y W. H. Prusoff, Biochem. Pharmacol., 22(23), 3099-3108, 1973). Alternatively, the affinity data for subunit α_2 are expressed as % inhibition at the concentrations of 10^{-5}M and 10^{-7}M. The results of these tests are given in Tables 1 and 2.

Table 1. Affinity for α_1-$GABA_A$ receptor

Compound	K_i (nM)
Example 1	88.6
Example 2	96.8
Example 3	110.0
Example 5	38.6
Example 8	623.0
Example 15	11.1
Example 18	28.3
Example 25	101.7
Example 28	11.7
Example 31	48.5
Example 32	31.0
Example 34	165.2
Example 35	41.2
Zaleplon	198.9

Table 2. Affinity for α_2-$GABA_A$ receptor

Compound	K_i (nM)	
Example 1	499.6	
Example 2	711.4	
Example 3	680.4	
Example 5	111.8	
Example 15	295.8	
Example 18	988.7	
Example 25	764.1	
Zaleplon	1302.5	
Compound	% Inhibition 10^{-5}M	% Inhibition 10^{-7}M
Example 28	96.4	29.0
Example 31	81.3	4.2
Example 32	89.0	21.0
Example 34	86.9	4.3
Example 35	91.5	18.9
Zaleplon	78.4	---

In vivo determination of predictive sedative-hypnotic action.

The *in vivo* effects of these compounds were assessed by a predictive sedation-hypnosis test in mice (D. J. Sanger et al., Eur. J. Pharmacol., 313, 35-42, 1996; and G. Griebel et al., Psychopharmacology, 146, 205-213, 1999).

Groups of 5-8 male CD1 mice, weighing 22-26 g at the time of test, were used. The test compounds were administered in single equimolecular intraperitoneal doses, suspended in 0.25% agar with one drop of Tween in a volume of 10 ml/kg. Control animals received the vehicle alone. Using an Actisystem DAS16 (Panlab, S.L., Spain) the crossings (number of counts) were recorded for each mouse at 5-min intervals during a period of 30 minutes after dosing. The inhibition percentage of crossings of treated animals versus control animals (the first 5 min were discarded) was calculated. The results of this test are given in Table 3.

Table 3. Determination of sedation-hypnosis in mice.

Compound	% Inhibition Motor Activity
Example 1	77.25
Example 2	77.25
Example 3	61.68
Example 5	79.06
Example 8	69.08
Example 18	68.55
Example 25	61.06
Example 28	94.19
Example 31	94.31
Example 32	91.57
Example 34	64.23
Example 35	91.21
Zaleplon	47.17

The present invention is illustrated by the following examples which are not intended to be limitative thereof.

Example 1: N-ethyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-acetamide

A mixture of 0.52 g (4.06 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 1.057 g (4.06 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-acetamide in 40 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 40 ml of dichloromethane and 20 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 15 ml of dichloromethane. The organic layers were washed with 20 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 225 mg of N-ethyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-acetamide as a yellow solid (yield 17%; m.p. 176-178°C).

^{1}H NMR(400 MHz, $CDCl_3$): δ 1.17 (3H, t, J= 6.8 Hz), 1.94 (3H, s), 3.82 (2H, q, J= 6.8 Hz), 7.31 (1H, d, J= 4.4 Hz), 7.47(1H, d, J= 7.6 Hz), 7.69 (1H, t, J= 7.6 Hz), 7.91 (1H, s), 7.96 (1H, d, J= 7.6 Hz), 8.82 (1H, s), 9.01 (1H, d, J= 4.4 Hz).

HPLC = 96.5%

Example 2: N-methyl-N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-acetamide

A mixture of 0.074 g (0.58 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.160 g (0.58 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-acetamide in 15 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 20 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which was chromatographied over silica gel (eluent: dichloromethane/methanol), giving 37 mg of N-metyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-acetamide as a yellowish-white solid (yield 29%).

^{1}H NMR(400 MHz, $CDCl_3$): δ 1.95 (3H, s), 3.35 (3H, s), 7.30 (1H, d, J= 4.8 Hz), 7.5 (1H, d J= 7.6 Hz), 7.68 (1H, t, J= 7.6 Hz), 7.93 (2H, m), 8.82 (1H, s), 9.01 (1H, d, J= 4.4 Hz).
MS (ES) *m/z* = 312 (MH+)
HPLC = 93%

Example 3: N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-propyl)-acetamide

A mixture of 0.051 g (0.4 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.1 g (0.4 mmol) of N-[3-[3-(dimethylamino)-

1-oxo-2-propenyl] phenyl]-N-(n-propyl)-acetamide in 5 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 4 ml of dichloromethane and 5 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 5 ml of dichloromethane. The organic layers were washed with 5 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 39 mg of N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-propyl)-acetamide as a yellow solid (yield 20%).

^{1}H NMR(400 MHz, $CDCl_3$): δ 0.84(3H, t, J= 7.6 Hz), 1.51 (2H, m), 1.87 (3H, s), 3.65 (2H, t, J= 7.6 Hz), 7.23 (1H, d, J= 4.4 Hz), 7.39 (1H, d J= 7.6 Hz), 7.61 (1H, t, J= 7.6 Hz), 7.83 (1H, s), 7.87 (1H, d, J= 7.6 Hz), 8.87 (1H, s), 8.93 (1H, d, J= 4.4 Hz).
HPLC = 80%

Example 4: N-(n-butyl)-N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-acetamide

A mixture of 0.067 g (0.52 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.150 g (0.52 mmol) of N-(n-butyl)-N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-acetamide in 5 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 4 ml of dichloromethane and 5 ml of saturated sodium bicarbonate solution. The two layers were separated, and

the aqueous layer was washed with 5 ml of dichloromethane. The organic layers were washed with 5 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which was chromatographied over silica gel (eluent: dichloromethane/methanol), giving 35 mg of N-(n-butyl)-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-acetamide as a yellowish-white solid (yield 19%).

^{1}H NMR(400 MHz, $CDCl_3$): δ 0.82 (3H, t, J= 7.6 Hz), 1.25 (2H, m), 1.45 (2H, m), 1.86 (3H, s), 3.68 (2H, t, J= 7.6 Hz), 7.27 (1H, d, J= 4.4 Hz), 7.4 (1H, d, J= 8 Hz), 7.62 (1H, t, J= 8 Hz), 7.85 (1H, s), 7.88 (1H, d, J= 8 Hz), 8.73 (1H, s), 8.93 (1H, d, J= 4.4 Hz).
MS (ES) *m/z* = 354 (MH+)
HPLC = 83%

Example 5: N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(2-propynyl)-acetamide

A mixture of 0.079 g (0.62 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.168 g (0.62 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-(2-propynyl)-acetamide in 13 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield

an oil which, in the presence of ethyl acetate, gave 58 mg of N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-N-(2-propynyl)-acetamide as a yellow solid (yield 28%).

^{1}H NMR(400 MHz, $CDCl_3$): δ 1.98 (3H, s), 2.25 (1H, s), 2.25 (2H, s) 7.31 (1H, d, J= 4.4 Hz), 7.60 (1H, d J= 7.6 Hz), 7.71 (1H, t, J= 7.6 Hz), 8.01-8.03 (2H, m), 8.83 (1H, s), 9.01 (1H, d, J= 4.4 Hz).

MS (ES) *m/z* = 336 (MH+)

HPLC = 97.7%

Example 6: 3-nitro-7-phenyl-pyrazolo[1,5-a]pyrimidine

A mixture of 0.100 g (0.78 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.137 g (0.78 mmol) of 3-dimethylamino-1-phenyl-propenone in 6 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which was chromatographied over silica gel (eluent: dichloromethane/methanol), giving 32 mg of 3-nitro-7-phenyl-pyrazolo[1,5-a]pyrimidine as a yellowish-white solid (yield 17%).

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.62-7.65 (3H, m), 7.66 (1H, d, J= 4.8 Hz), 8.03-8.05 (2H, m), 9.05 (1H, d, J= 4.8 Hz), 9.09 (1H, s).

HPLC = 85%

Example 7: 3-nitro-7-(2-trifluoromethyl-phenyl)-pyrazolo [1,5-a]pyrimidine

A mixture of 0.100 g (0.78 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.189 g (0.78 mmol) of 3-dimethylamino-1-(2-trifluoromethyl-phenyl)-propenone in 6 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which was chromatographied over silica gel (eluent: dichloromethane/methanol), giving 134 mg of 3-nitro-7-(2-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine as a yellowish-white solid (yield 56%; m.p. 195-197°C).

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.19 (1H, d, J= 4.8 Hz), 7.51-7.54 (1H, m), 7.78-7.80 (1H, m), 7.91-7.94 (1H, m), 8.73 (1H, s), 9.02 (1H, d, J= 4.4 Hz).
HPLC = 89.4%

Example 8: 3-nitro-7-(3-trifluoromethyl-phenyl)-pyrazolo [1,5-a]pyrimidine

A mixture of 0.100 g (0.78 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.189 g (0.78 mmol) of 3-dimethylamino-1-(3-trifluoromethyl-phenyl)-propenone in 6 ml of glacial

acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which was chromatographied over silica gel (eluent: dichloromethane/methanol), giving 131 mg of 3-nitro-7-(3-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine as a yellowish-white solid (yield 54.5%; m.p. 159-161°C).

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.32 (1H, d, J= 4.8 Hz), 7.77 (1H, t, J= 7.6 Hz), 7.91 (1H, d, J= 7.6 Hz), 8.22 (1H, d, J= 7.6 Hz), 8.23 (1H, s), 8.84 (1H, s), 9.02 (1H, d, J= 4.4 Hz).

HPLC = 88.5%

Example 9: 3-nitro-7-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine

A mixture of 0.100 g (0.78 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.189 g (0.78 mmol) of 3-dimethylamino-1-(4-trifluoromethyl-phenyl)-propenone in 6 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of

dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which was chromatographied over silica gel (eluent: dichloromethane/methanol), giving 168 mg of 3-nitro-7-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine as a yellowish-white solid (yield 70%; m.p. 191-193°C).

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.29 (1H, d, J= 4.8 Hz), 7.88 (2H, d, J= 8 Hz), 8.12 (2H, d, J= 8 Hz), 8.84 (1H, s), 9.02 (1H, d, J= 4.4 Hz).
HPLC = 86.9%

Example 10: 7-furan-2-yl-3-nitro-pyrazolo[1,5-a]pyrimidine

A mixture of 0.100 g (0.78 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.129 g (0.78 mmol) of 3-dimethylamino-1-furan-2-yl-propenone in 6 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which was chromatographied over silica gel (eluent: dichloromethane/ methanol), giving 152 mg of 7-furan-2-yl-3-nitro-pyrazolo[1,5-a]pyrimidine as a yellowish-white solid (yield 85%; m.p. 235-237°C).

^{1}H NMR(400 MHz, $CDCl_3$): δ 6.79 (1H, dd, J= 4.8 and 1.6 Hz), 7.64 (1H, d, J= 4.4 Hz), 7.81 (1H, d, J= 1.2 Hz), 8.26 (1H, d, J= 3.2 Hz), 8.87 (1H, s), 8.94 (1H, d, J= 4.8 Hz).

HPLC = 93.2%

Example 11: 3-nitro-7-thiophen-2-yl-pyrazolo[1,5-a]pyrimidine

A mixture of 0.100 g (0.78 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.142 g (0.78 mmol) of 3-dimethylamino-1-thiophen-2-yl-propenone in 6 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 91 mg of 3-nitro-7-thiophen-2-yl-pyrazolo[1,5-a]pyrimidine as a yellow solid (yield 47%; m.p. 235-237°C).

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.34 (1H, dd, J= 3.6 and 1.2 Hz), 7.56 (1H, d, J= 4.8 Hz), 7.88 (1H, dd, J= 5 and 1.2 Hz), 8.41 (1H, dd, J= 4 and 1.2 Hz), 8.90 (1H, d, J= 4.8 Hz), 8.91 (1H, s).

MS (ES) *m/z* = 247 (MH+)

HPLC = 93.3%

Example 12: 3-nitro-7-pyridin-2-yl-pyrazolo[1,5-a] pyrimidine

A mixture of 0.100 g (0.78 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.138 g (0.78 mmol) of 3-dimethylamino-1-pyridin-2-yl-propenone in 6 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 45 mg of 3-nitro-7-pyridin-2-yl-pyrazolo[1,5-a]pyrimidine as a yellow solid (yield 24%).

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.55 (1H, dd, J= 4.8 and 2.4 Hz), 7.98 (1H, t, J= 7.6 Hz), 8.07 (1H, d, J= 4.8 Hz), 8.86 (1H, d, J= 4.8 Hz), 8.89 (1H, s), 8.95 (1H, d, J= 8 Hz), 9.06 (1H, d, J= 4 Hz).
MS (ES) *m/z* = 242 (MH+)
HPLC = 98.4%

Example 13: 3-nitro-7-pyridin-3-yl-pyrazolo[1,5-a] pyrimidine

A mixture of 0.100 g (0.78 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.138 g (0.78 mmol) of 3-dimethylamino-1-pyridin-3-yl-propenone in 6 ml of glacial acetic acid

was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 99 mg of 3-nitro-7-pyridin-3-yl-pyrazolo[1,5-a]pyrimidine as a yellow solid (yield 47%; m.p. 302-303°C).

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.65-7.69 (1H, m), 7.78 (1H, d, J= 4.4 Hz), 8.45-8.48 (1H, m), 8.81 (1H, dd, J= 4.8 and 1.6 Hz), 9.01 (1H, d, J= 4.8 Hz), 9.11 (1H, s), 9.16 (1H, dd, J= 2.4 and 0.8 Hz).
HPLC = 94.1%

Example 14: 3-nitro-7-pyridin-4-yl-pyrazolo[1,5-a] pyrimidine

A mixture of 0.105 g (0.82 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.144 g (0.82 mmol) of 3-dimethylamino-1-pyridin-4-yl-propenone in 8 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to

dryness to yield an oil which was chromatographied over silica gel (eluent: dichloromethane/methanol), giving 68 mg of 3-nitro-7-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine as a yellow solid (yield 34%; m.p. 241-244°C).

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.7 (1H, d, J= 4.4 Hz), 7.98-8.00 (2H, m), 8.84-8.86 (2H, m), 9.10 (1H, d, J= 4.4 Hz), 9.11 (1H, s).
MS (ES) *m/z* = 242 (MH+)
HPLC = 83.6 %

Example 15: N-ethyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-methanesulfonamide

A mixture of 0.0086 g (0.068 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.02 g (0.068 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-methanesulfonamide in 1.5 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 15 mg of N-ethyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-methanesulfonamide as a yellow solid (yield 61%).

^{1}H NMR(400 MHz, DMSO-d_6): δ 1.23 (3H, t, J= 6.8 Hz), 2.96 (3H, s), 3.83 (2H, q, J= 7.2 Hz), 7.31 (1H, d, J= 4.4 Hz), 7.62 (1H, d, J= 7.6 Hz), 7.67 (1H, t, J= 7.6 Hz), 7.98 (1H, d, J= 7.6 Hz), 8.05 (1H, s), 8.82 (1H, s), 9.01 (1H, d, J= 4.4 Hz).
MS (ES) *m/z* = 362 (MH+)
HPLC = 92.1%

Example 16: N-ethyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-4-methoxy-benzenesulfonamide

A mixture of 0.1 g (0.79 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.305 g (0.068 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-4-methoxy-benzenesulfonamide in 5 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 117 mg of N-ethyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-4-methoxy-benzenesulfonamide as a yellow solid (yield 33%; m.p. 209-211°C).

^{1}H NMR(400 MHz, DMSO-d_6): δ 1.00 (3H, t, J= 7.2 Hz), 3.59 (2H, q, J= 7.2 Hz), 3.83 (1H, s), 7.10-7.13 (2H, m), 7.35(1H, d, J= 7.6 Hz), 7.54-7.56 (2H, m), 7.60 (1H, d,

J= 4.4 Hz), 7.62 (1H, t, J= 8 Hz), 7.78 (1H, s), 8.00 (1H, d, J= 8 Hz), 9.05 (1H, d, J= 4.4 Hz) 9.06 (1H, s).
HPLC = 90.4%

Example 17: N-ethyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-benzenesulfonamide

A mixture of 0.121 g (0.958 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.340 g (0.958 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-benzene-sulfonamide in 5 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 150 mg of N-ethyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-benzene-sulfonamide as a yellow solid (yield 38%; m.p. 189-191°C).

^{1}H NMR(400 MHz, DMSO-d_6): δ 1.01 (3H, t, J= 7.2 Hz), 3.62 (2H, q, J= 7.2 Hz), 7.36(1H, d, J= 7.2 Hz), 7.57 (1H, d, J= 4.8 Hz), 7.60-7.64 (5H, m), 7.71-7.73 (1H, m), 7.76 (1H, s), 8.00 (1H, d, J= 7.6 Hz), 9.04 (1H, d, J= 4.8 Hz), 9.07 (1H, s).
HPLC = 98.9%

Example 18: N-methyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-methanesulfonamide

A mixture of 0.076 g (0.60 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.160 g (0.60 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-methanesulfonamide in 5 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 107 mg of N-methyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-4-methanesulfonamide as a yellow solid (yield 54%).

^{1}H NMR(400 MHz, DMSO-d_6): δ 2.93 (3H, s,), 3.42 (3H, s), 7.31 (1H, d, J= 4.8 Hz), 7.64-7.65 (2H, m), 7.91-7.93 (1H, m), 8.08 (1H, s), 8.81 (1H, s), 8.99 (1H, d, J= 4.8 Hz).
MS (ES) *m/z* = 348 (MH+)
HPLC = 91.7%

Example 19: N-(n-butyl)-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-4-methoxy-benzenesulfonamide

A mixture of 0.049 g (0.38 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.160 g (0.52 mmol) of N-(n-butyl)-N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-4-methoxy-benzenesulfonamide in 5 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by

reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 90 mg of N-(n-butyl)-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-4-methoxy-benzenesulfonamide as a yellow solid (yield 49%; m.p. 189-190°C).

^{1}H NMR(400 MHz, DMSO-d_6): δ 0.82 (3H, t, J= 7.2 Hz), 1.26-1.33 (4H, m), 3.54 (2H, t, J= 6.4 Hz), 3.83 (3H, s), 7.11 (2H, d, J= 6.8 Hz), 7.35 (1H, d J= 7.2 Hz), 7.54 (2H, d, J= 6.8 Hz), 7.58 (1H, d, J= 4.8 Hz), 7.62 (1H, t, J= 8 Hz), 7.77 (1H, s), 7.99 (1H, d, J= 7.2 Hz), 9.04 (1H, d, J= 4.4 Hz), 9.05 (1H, s).
MS (ES) *m/z* = 482 (MH+)
HPLC = 98.4%

Example 20: N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-propyl)-4-methoxy-benzenesulfonamide

A mixture of 0.067 g (0.52 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.210 g (0.52 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-(n-propyl)-4-methoxy-benzene-sulfonamide in 5 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The

two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 139 mg of N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-propyl)-4-methoxy-benzenesulfonamide as a yellow solid (yield 57%; m.p. 184-185°C).

^{1}H NMR(400 MHz, DMSO-d_6): δ 0.84 (3H, t, J= 7.2 Hz), 1.32-1.37 (2H, m), 3.50 (2H, t, J= 7.2 Hz), 3.83 (3H, s), 7.11 (2H, d, J= 6.8 Hz), 7.36 (1H, d J= 7.2 Hz), 7.53 (2H, d, J= 6.8 Hz), 7.58 (1H, d, J= 4.8 Hz), 7.62 (1H, t, J= 8 Hz), 7.77 (1H, s), 7.99 (1H, d, J= 7.6 Hz), 9.04 (1H, d, J= 4.8 Hz), 9.05 (1H, s).
MS (ES) *m/z* = 468 (MH+)
HPLC = 98.9 %

Example 21: N-methyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-4-methoxy-benzenesulfonamide

A mixture of 0.027 g (0.21 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.80 g (0.21 mmol) of N-methyl-N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-4-methoxy-benzene-sulfonamide in 5 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate.

The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 50 mg of N-methyl-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-4-methoxy-benzenesulfonamide as a yellow solid (yield 53%; m.p. 205-206°C).

^{1}H NMR(400 MHz, DMSO-d_6): δ 3.15 (3H, s), 3.83 (3H, s), 7.11 (2H, d, J= 6.8 Hz), 7.36 (1H, d J= 7.2 Hz), 7.49 (2H, d, J= 6.8 Hz), 7.59 (1H, d, J= 4.8 Hz), 7.60 (1H, t, J= 7.8 Hz), 7.84 (1H, s), 7.96(1H, d, J= 7.6 Hz), 9.04 (1H, d, J= 4.4 Hz), 9.07 (1H, s).
MS (ES) *m/z* = 440 (MH+)
HPLC = 97%

Example 22: N-(n-butyl)-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-4-benzenesulfonamide

A mixture of 0.103 g (0.80 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.31 g (0.52 mmol) of N-(n-butyl)-N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-benzenesulfonamide in 5 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 185 mg of N-(n-butyl)-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-benzenesulfonamide as a yellow solid (yield 51%; m.p. 159-160°C).

^{1}H NMR(400 MHz, DMSO-d_6): δ 0.82 (3H, t, J= 7.2 Hz), 1.26-1.33 (4H, m), 3.57 (2H, t, J= 6.4 Hz), 7.38 (1H, d J= 8 Hz), 7.55 (1H, d, J= 4.8 Hz), 7.59-7.63 (5H, m), 7.70-7.72 (1H, m), 7.75 (1H, s), 7.99 (1H, d, J= 8 Hz), 9.03 (1H, d, J= 4.8 Hz), 9.05 (1H, s).
MS (ES) *m/z* = 452 (MH+)
HPLC = 100%

Example 23: N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-propyl)-benzenesulfonamide

A mixture of 0.117 g (0.91 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.340 g (0.91 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-(n-propyl)-benzenesulfonamide in 5 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 154 mg of N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-N-(n-propyl)-benzenesulfonamide as a yellow solid (yield 39%; m.p. 154-156°C).

^{1}H NMR(400 MHz, DMSO-d_6): δ 0.84 (3H, t, J= 7.2 Hz), 1.3-1.39 (2H, m), 3.53 (2H, t, J= 6.8 Hz), 7.38 (1H, d J= 8 Hz), 7.56 (1H, d, J= 4.8 Hz), 7.60-7.64 (5H, m),

7.71-7.74 (1H, m), 7.75 (1H, s), 8.00 (1H, d, J= 8.4 Hz), 9.04 (1H, d, J= 4.8 Hz), 9.06 (1H, s).
MS (ES) *m/z* = 438 (MH+)
HPLC = 100%

Example 24: N-methyl-N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-4-benzenesulfonamide

A mixture of 0.78 g (0.61 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.21 g (0.52 mmol) of N-methyl-N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-benzenesulfonamide in 5 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 108 mg of N-methyl-N-[3-(3-nitro-pyrazolo [1,5-a]pyrimidin-7-yl)-phenyl]-benzenesulfonamide as a yellow solid (yield 43%; m.p. 177-179°C).

^{1}H NMR(400 MHz, DMSO-d_6): δ 3.19 (3H, s), 7.39 (1H, d, J= 8 Hz), 7.57-7.63 (6H, m), 7.71 (1H, t, J= 6.8 Hz), 7.82 (1H, s), 7.95 (1H, d, J= 8 Hz), 9.04 (1H, d, J= 4.8 Hz), 9.07 (1H, s).
MS (ES) *m/z* = 409 (MH+)
HPLC = 98.2%

Example 25: N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-propyl)-methanesulfonamide

A mixture of 0.078 g (0.61 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.19 g (0.61 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-(n-propyl)-methanesulfonamide in 5 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 118 mg of N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-N-(n-propyl)-methanesulfonamide as a yellow solid (yield 53%; m.p. 165-167°C).

^{1}H NMR(400 MHz, DMSO-d_6): δ 0.90 (3H, t, J= 7.2 Hz), 1.42-1.47 (2H, m), 3.07 (3H, s), 3.68 (2H, t, J= 7.2 Hz), 7.67-7.72 (2H, m), 7.75 (1H, d, J= 4.4 Hz), 8.05-8.08 (1H, m), 8.09 (1H, s), 9.10 (1H, d, J= 4.4 Hz), 9.14 (1H, s).
MS (ES) *m/z* = 376 (MH+)
HPLC = 98.3%

Example 26: N-(n-butyl)-N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-methanesulfonamide

A mixture of 0.079 g (0.61 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.20 g (0.61 mmol) of N-(n-butyl)-N-[3-[3-

(dimethylamino)-1-oxo-2-propenyl]phenyl]-methanesulfonamide in 5 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 135 mg of N-(n-butyl)-N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-methanesulfonamide as a yellow solid (yield 56%; m.p. 153-155°C).

^{1}H NMR(400 MHz, DMSO-d_6): δ 0.84 (3H, t, J= 6.8 Hz), 1.28-1.39 (4H, m), 3.03 (3H, s), 3.68 (2H, t, J= 6.8 Hz), 7.63-7.69 (2H, m), 7.71 (1H, d, J= 4.8 Hz), 8.01-8.06 (1H, m), 8.07 (1H, s), 9.07 (1H, d, J= 4.4 Hz), 9.09 (1H, s).
MS (ES) *m/z* = 390 (MH+)
HPLC = 95.1%

Example 27: 1-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-pyrrolidin-2-one

A mixture of 0.100 g (0.78 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.202 g (0.78 mmol) of 1-[3-(3-dimethylamino-acryloyl)-phenyl]-pyrrolidin-2-one in 8 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium

bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which was chromatographied over silica gel (eluent: dichloromethane/methanol), giving 73 mg of 1-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-pyrrolidin-2-one as a yellow solid (yield 29%; m.p. 226-228°C).

^{1}H NMR(400 MHz, $CDCl_3$): δ 2.21-2.25 (2H, m), 2.66 (2H, t, J= 8 Hz), 3.94 (2H, t, J= 7.2 Hz), 7.30 (1H, d, J= 4.4 Hz), 7.6 (1H, t, J= 8 Hz), 7.72-7.77 (2H, m), 8.47-8.48 (1H, m), 8.82 (1H, s), 8.97 (1H, d, J= 4.4 Hz).
MS (ES) *m/z* = 324 (MH+)
HPLC = 100%

Example 28: N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(prop-2-inyl)-methanesulfonamide

0.042 g (0.33 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.1 g (0.33 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl] phenyl]-N-(n-prop-2-inyl)-methane-sulfonamide dissolved in 5 ml of glacial acetic acid were refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 4 ml of dichloromethane and 5 ml of saturated sodium bicarbonate. The two layers were separated, and the aqueous layer was washed with 5 ml of dichloromethane. The organic layers were washed with 5 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield

an oil which, in the presence of ethyl acetate, gave 62 mg of N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-N-(prop-2-inyl)-methane-sulfonamide as a yellow solid (yield 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.55 (1H, t, J= 2.4 Hz), 3.11 (3H, s), 4.54 (2H, s), 7.31 (1H, d, J= 4.8 Hz), 7.67 (1H, t, J= 8 Hz), 7.89-7.92 (1H, m), 7.99-8.02 (1H, m), 8.26-8.28 (1H, m), 8.83 (1H, s), 9 (1H, d, J= 4.4 Hz).
MS (ES) *m/z* = 372 (MH+)
HPLC = 88.5%

Example 29: N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-propyl)-ethanesulfonamide

0.028 g (0.26 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.07 g (0.26 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-(n-propyl)-ethanesulfonamide dissolved in 5 ml of glacial acetic acid were refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 4 ml of dichloromethane and 5 ml of saturated sodium bicarbonate. The two layers were separated, and the aqueous layer was washed with 5 ml of dichloromethane. The organic layers were washed with 5 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 24 mg of N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-N-(propyl)-ethanesulfonamide as a yellow solid (yield 29%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (3H, t, J= 7.6 Hz), 1.42 (3H, T, J= 7.6 Hz), 1.54-1.60 (2h, m), 3.06-3.12 (2H, q,

J= 7.6 Hz), 3.74 (2H, T, J= 7.6 Hz), 7.31 (1H, d, J= 4.4 Hz), 7.61-7.67 (2H, m), 7.95-7.98 (1H, m), 8.06-8.07 (1H, m),8.83 (1H, s), 8.98-8.99 (1H, d, J= 4.4 Hz).
MS (ES) m/z = 390 (MH+)
HPLC = 96.1%

Example 30: N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(ethyl)-ethanesulfonamide

0.029 g (0.23 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.07 g (0.23 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-(ethyl)-ethanesulfonamide dissolved in 5 ml of glacial acetic acid were refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 4 ml of dichloromethane and 5 ml of saturated sodium bicarbonate. The two layers were separated, and the aqueous layer was washed with 5 ml of dichloromethane. The organic layers were washed with 5 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 21 mg of N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-N-(n-ethyl)-ethanesulfonamide as a yellow solid (yield 25%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, t, J= 7.2 Hz), 1.4 (6H, d, J= 7.2 Hz), 3.28 (1H, m), 3.86 (2H, t, J= 6.8 Hz), 7.31 (1H, d, J= 4.4 Hz), 7.63-7.65 (2H, m), 7.94-7.97 (1H, m), 8.06-8.08 (1H, m), 8.82 (1H, s), 8.98-8.99 (1H, d, J= 4.4 Hz).
MS (ES) m/z = 376 (MH+)
HPLC = 96.4%

Example 31: N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-prop-2-inyl)-propane-2-sulfonamide

0.048 g (0.37 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.125 g (0.37 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-(n-prop-2-inyl)-propane-2-sulfonamide dissolved in 5 ml of glacial acetic acid were refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 4 ml of dichloromethane and 5 ml of saturated sodium bicarbonate. The two layers were separated, and the aqueous layer was washed with 5 ml of dichloromethane. The organic layers were washed with 5 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 37 mg of N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-N-(n-prop-2-inyl)-propane-2-sulfonamide as a yellow solid (yield 25%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (6H, d, J= 6.4 Hz), 2.43 (1H, s), 3.44-3.5 (1H, m), 4.55 (2H, s), 7.31 (1H, d, J= 4.8 Hz), 7.65 (1H, t, J= 7.6 Hz), 7.80-7.82 (1H, m), 7.99 (1H, d, J= 7.6 Hz), 8.21 (1H, s),8.83(1H, s), 8.99 (1H, d, J= 4.4 Hz).
MS (ES) m/z = 400 (MH+)
HPLC = 100%

Example 32: N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-ethanesulfonamide

0.043 g (0.34 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.1 g (0.34 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl] phenyl]-N-methyl-ethanesulfonamide dissolved in 5 ml of glacial acetic acid were refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 4 ml of dichloromethane and 5 ml of saturated sodium bicarbonate. The two layers were separated, and the aqueous layer was washed with 5 ml of dichloromethane. The organic layers were washed with 5 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 38 mg of N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-N-(methyl)-ethanesulfonamide as a yellow solid (yield 31%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (3H, t, J= 7.2 Hz), 3.11 (2H, q, J= 7.6 Hz), 3.44 (3H, s), 7.3 (1H, d, J= 4.4 Hz), 7.59-7.67 (2H, m), 7.88-7.92 (1H, m), 8.08-8.09 (1H, m), 8.83 (1H, s), 8.99 (1H, d, J= 4.8 Hz).
MS (ES) m/z = 362 (MH+)
HPLC = 96.1%

Example 33: N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-butyl)-ethanesulfonamide

0.026 g (0.21 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.07 g (0.21 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-(n-butyl)-ethanesulfonamide dissolved in 5 ml of glacial acetic acid were refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 4 ml of dichloromethane and 5 ml of saturated sodium bicarbonate.

The two layers were separated, and the aqueous layer was washed with 5 ml of dichloromethane. The organic layers were washed with 5 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 34 mg of N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-N-(n-butyl)-ethanesulfonamide as a yellow solid (yield 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (3H, t, J= 7.2 Hz), 1.34-1.43 (5H, m), 1.49-1.52 (2H, m), 3.09 (2H, q, J= 7.2 Hz), 3.78 (2H, t, J= 7.2 Hz), 7.31 (1H, d, J= 4.4 Hz), 7.61-7.67 (2H, m), 7.95-7.98 (1H, m), 8.06 (1H, s),8.23 (1H, s), 8.99 (1H, d, J= 4.4 Hz).
MS (ES) m/z = 404 (MH+)
HPLC = 99.1%

Example 34: 7-(3-(2-isothiazolidinyl-1,1-dioxide)-phenyl)-3-nitro-pyrazolo[1,5-a]pyrimidine

0.043 g (0.34 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.1 g (0.34 mmol) of 3-dimethylamino-1-[3-(1,1-dioxo-isothiazolydin-2-yl)-phenyl]-propenone dissolved in 5 ml of glacial acetic acid were refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 4 ml of dichloromethane and 5 ml of saturated sodium bicarbonate. The two layers were separated, and the aqueous layer was washed with 5 ml of dichloromethane. The organic layers were washed with 5 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 64 mg of 7-[3-(2-isothiazolydinyl-1,1-

dioxide)-phenyl)-3-nitro-pyrazolo[1,5-a]pyrimidine as a yellow solid (yield 52%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.47-2.51 (2H, m), 3.61 (2H, t, J= 7.2 Hz), 3.86 (2H, t, J= 6.4 Hz), 7.55 (1H, d, J= 7.6 Hz), 7.67 (1H, t, J= 8 Hz), 7.7 (1H, d, J= 4.4 Hz), 7.78-7.81 (2H, m), 9.1 (1H, d, J= 4 Hz), 9.14 (1H, s).
MS (ES) m/z = 360 (MH+)
HPLC = 86.9%

Example 35: N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-propane-2-sulfonamide

0.062 g (0.48 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.15 g (0.48 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-propane-2-sulfonamide dissolved in 5 ml of glacial acetic acid were refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 4 ml of dichloromethane and 5 ml of saturated sodium bicarbonate. The two layers were separated, and the aqueous layer was washed with 5 ml of dichloromethane. The organic layers were washed with 5 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 122 mg of N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-N-methyl-propane-2-sulfonamide as a yellow solid (yield 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (6H, d, J= 7.2 Hz), 3.36-3.341 (1H, m), 3.46 (3H, s), 7.3 (1H, d, J= 4.4 Hz), 7.59-7.67 (2H, m), 7.85-7.88 (1H, m), 8.10-8.12 (1H, m), 8.82 (1H, s), 8.97-8.99 (1H, d, J= 4.4 Hz).

MS (ES) m/z = 376 (MH+)
HPLC = 91.6%

Example 36: N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-propane-2-sulfonamide

0.067 g (0.52 mmol) de 4-nitro-2H-pyrazol-3-ylamine and 0.17 g (0.52 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-propane-2-sulfonamide dissolved in 5 ml of glacial acetic acid were refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 4 ml of dichloromethane and 5 ml of saturated sodium bicarbonate. The two layers were separated, and the aqueous layer was washed with 5 ml of dichloromethane. The organic layers were washed with 5 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 97 mg of N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-propane-2-sulfonamide as a yellow solid (yield 47%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, t, J= 7.2 Hz), 1.4 (6H, d, J= 7.2 Hz), 3.28 (1H, m), 3.86 (2H, t, J= 6.8 Hz), 7.31 (1H, d, J= 4.4 Hz), 7.63-7.65 (2H, m), 7.94-7.97 (1H, m), 8.06-8.08 (1H, m), 8.82 (1H, s), 8.98-8.99 (1H, d, J= 4.4 Hz).
MS (ES) m/z = 390 (MH+)
HPLC = 93.9%

Example 37: N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-butyl)-propane-2-sulfonamide

0.032 g (0.26 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.09 g (0.26 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-(n-butyl)-propane-2-sulfonamide dissolved in 5 ml of glacial acetic acid were refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 4 ml of dichloromethane and 5 ml of saturated sodium bicarbonate. The two layers were separated, and the aqueous layer was washed with 5 ml of dichloromethane. The organic layers were washed with 5 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 49 mg of N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-N-(n-butyl)-propane-2-sulfonamide as a yellow solid (yield 46%).

^{1}H NMR(400 MHz, $CDCl_3$): δ 0.89(3H, t, J= 7.6 Hz), 1.36 (2H, m), 1.40 (2H, d, J= 6.8 Hz), 1.51 (2H, m), 3.27 (1H, m), 3.80 (2H, t, J= 7.6 Hz), 7.31 (1H, d, J= 4.4 Hz), 7.63-7.65 (2H, m), 7.94-7.96 (1H, m), 8.09(1H, m), 8.82 (1H, s), 8.89 (1H, d, J= 4.4 Hz).
MS (ES) *m/z* = 418 (MH+)
HPLC = 100%

Example 38: N-[3-(3-nitro-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-(n-propyl)-propane-2-sulfonamide

0.064 g (0.50 mmol) of 4-nitro-2H-pyrazol-3-ylamine and 0.17 g (0.50 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-(n-propyl)-propane-2-sulfonamide dissolved in 5 ml of glacial acetic acid were refluxed for 8 hours and then the solvent was removed by reduced

pressure distillation. To the resulting residue were added 4 ml of dichloromethane and 5 ml of saturated sodium bicarbonate. The two layers were separated, and the aqueous layer was washed with 5 ml of dichloromethane. The organic layers were washed with 5 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 116 mg of N-[3-(3-nitro-pyrazolo[1,5-a] pyrimidin-7-yl)-phenyl]-N-(n-propyl)-propane-2-sulfonamide as a yellow solid (yield 57%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (3H, t, J= 7.6 Hz), 1.4 (6H, d, J= 7.2 Hz), 1.53-1.58 (2H, m), 3.26-3.29 (1H, m), 3.76 (2H, t, J= 7.6 Hz), 7.31 (1H, d, J= 4.8 Hz), 7.63-7.65 (2H, m), 7.94-7.96 (1H, m), 8.08-8.09 (1H, m), 8.82 (1H,s).

MS (ES) m/z = 404 (MH+)

HPLC = 94.5%

Example 39: 5 mg tablets

Compound of Example 1	5.0	mg
Colloidal silicon dioxide	0.6	mg
Croscarmellose sodium	12.0	mg
Talc	4.0	mg
Magnesium stearate	1.5	mg
Polysorbate 80	1.0	mg
Lactose	75.0	mg
Hydroxypropyl methylcellulose	3.0	mg
Polyethylene glycol 4000	0.5	mg
Titanium dioxide E171	1.5	mg
Microcrystalline cellulose q.s. to	125.0	mg

Example 40: 10 mg capsules

Compound of Example 1	10.0	mg
Colloidal silicon dioxide	0.6	mg
Crospovidone	12.0	mg
Talc	4.0	mg
Magnesium stearate	1.5	mg
Lauryl sulfate sodium	1.5	mg
Lactose	77.0	mg
Gelatin	28.5	mg
Titanium dioxide E171	1.5	mg
Indigotin E132	0.02	mg
Microcrystalline cellulose q.s. to	155.0	mg

Example 41: oral drops

Compound of Example 1	0.5	g
Propylene glycol	10.0	g
Glycerin	5.0	g
Saccharin sodium	0.1	g
Polysorbate 80	1.0	g
Lemon flavor	0.2	g
Ethanol	25.0	mL
Purified water q.s. to	100.0	mL

Example 42: 2.5 mg tablets

Compound of Example 28	2.5	mg
Colloidal silicon dioxide	0.6	mg
Croscarmellose sodium	12.0	mg
Talc	4.0	mg
Magnesium stearate	1.5	mg
Polysorbate 80	1.0	mg
Lactose	75.0	mg

Hydroxypropyl methylcellulose	3.0	mg
Polyethylene glycol 4000	0.5	mg
Titanium dioxide E171	1.5	mg
Microcrystalline cellulose q.s. to	125.0	mg

Example 43: 5 mg capsules

Compound of Example 28	5.0	mg
Colloidal silicon dioxide	0.6	mg
Crospovidone	12.0	mg
Talc	4.0	mg
Magnesium stearate	1.5	mg
Lauryl sulfate sodium	1.5	mg
Lactose	77.0	mg
Gelatin	28.5	mg
Titanium dioxide E171	1.5	mg
Indigotin E132	0.02	mg
Microcrystalline cellulose q.s. to	155.0	mg

Example 44: oral drops

Compound of Example 28	0.25	g
Propylene glycol	10.0	g
Glycerin	5.0	g
Saccharin sodium	0.1	g
Polysorbate 80	1.0	g
Lemon flavor	0.2	g
Ethanol	25.0	mL
Purified water q.s. to	100.0	mL